

AD_____

Award Number: DAMD17-01-1-0748

TITLE: Alcohol and Wine in Health and Disease Conference

PRINCIPAL INVESTIGATOR: Rashid Shaikh, Ph.D.

CONTRACTING ORGANIZATION: New York Academy of Sciences
New York, New York 10021-7289

REPORT DATE: October 2001

TYPE OF REPORT: Final Proceedings

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

20021105 002

REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)**2. REPORT DATE**
October 2001**3. REPORT TYPE AND DATES COVERED**

Final Proceedings (26 Apr 01 - 25 Sep 01)

4. TITLE AND SUBTITLE

Alcohol and Wine in Health and Disease Conference

5. FUNDING NUMBERS

DAMD17-01-1-0748

6. AUTHOR(S)

Rashid Shaikh, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)New York Academy of Sciences
New York, New York 10021-7289**E-Mail:** rshaikh@nyas.org**8. PERFORMING ORGANIZATION
REPORT NUMBER****9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012**10. SPONSORING / MONITORING
AGENCY REPORT NUMBER****11. SUPPLEMENTARY NOTES****12a. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE**13. ABSTRACT (Maximum 200 Words)**

None provided.

14. SUBJECT TERMS

alcohol, wine, health, disease

15. NUMBER OF PAGES

13

16. PRICE CODE**17. SECURITY CLASSIFICATION
OF REPORT**

Unclassified

**18. SECURITY CLASSIFICATION
OF THIS PAGE**

Unclassified

**19. SECURITY CLASSIFICATION
OF ABSTRACT**

Unclassified

20. LIMITATION OF ABSTRACT

Unlimited

Table of Contents

Cover	
SF 298	
Table of Contents	
Introduction	1
The Epidemiological Evidence	1
What's in the Glass? A Quick Course in Wine Chemistry	4
How Phenols and Alcohol Work	6
Should I Drink, Doctor?	9
Appendices	



Alcohol and Wine in Health and Disease

A summary report on a multidisciplinary conference sponsored by the New York Academy of Sciences.

The conference was organized by Dipak K. Das, Ph.D. (Cardiovascular Research Center, University of Connecticut Health Center, Farmington, CT), and Fulvio Ursini, M.D. (Department of Biochemistry, University of Padova, Italy). It was held during April 26-29, 2001 in Palo Alto, CA. This report was written by Nada Rose Mangialetti.

In recent years the possible beneficial role of mild-to-moderate alcohol consumption in the prevention of heart disease has gained attention in the scientific community as well as in the media. Several studies suggest that the consumption of wine, particularly red wine, imparts a greater benefit in the prevention of coronary heart disease than that obtained from drinking other alcoholic beverages. These reports gave rise to what is now popularly termed the "French Paradox" - a lower incidence of cardiovascular disease in France despite a diet rich in saturated fats.

Despite the popular interest, however, there has been no reliable and comprehensive scientific evaluation of the subject. This prompted the Academy to sponsor this conference. The conference provided a forum for discussion and dissemination of information about the potential effect of wine consumption as a preventative measure against cardiovascular diseases and the health risks associated with excessive alcohol intake. The conference also provided an opportunity for investigators active in the field to consider objectively the possible mechanisms by which wine or alcohol may protect against cardiovascular disease.

Topics covered at the conference included:

1. a review of the latest epidemiological evidence about the relation between alcohol and cardiovascular disease
2. a series of detailed analyses of the components of wine that may account for its healthful benefits
3. a discussion of theories about just how wine and other alcoholic drinks work to protect the heart or may help in fighting cancer and other degenerative diseases
4. an analysis of the risks of drinking (i.e., the possibility of alcoholism and alcohol-induced disease and organ-damage) versus the health benefits of drinking

1. THE EPIDEMIOLOGICAL EVIDENCE

Arthur Klatsky, M.D., a cardiology consultant to Kaiser Permanente Medical Center, says that the harm that results from heavy drinking and the benefit that comes from light drinking have been known for as long as wine has been around. But it wasn't until the rise of epidemiology that systematic investigations started to accumulate scientific data. In 1926, Raymond Pearl of the Johns Hopkins University plotted the relationship between drinking and mortality, and came up with a J-shaped curve. Heavy drinkers died young; abstainers were in the middle; moderate drinkers died old. That J-shaped curve has since become classic in epidemiological studies of

alcohol and mortality, as well as specific forms of coronary heart disease such as cardiomyopathy, high blood pressure, atrial fibrillation, hemorrhage stroke, and atherosclerosis.

Heavy drinking is associated with increased rates of all the coronary heart diseases, plus cirrhosis of the liver, and mouth, pharynx, larynx, esophageal and liver cancers. Meir Stampfer, an epidemiologist at Harvard, points out that because chronic alcoholics tend not to volunteer for epidemiological studies, the degree of harm associated with heavy drinking is probably underestimated.

Dr. Stampfer also explains that meta-analysis (a strategy for statistical analysis in which data from a number of separate studies can be examined simultaneously to arrive at an overarching conclusion) reveals a 9% to 10% increase in risk of breast cancer for women who engage in light drinking. However, the overall mortality for these women is lower than for women who do not drink at all or for those who are heavy drinkers. He also suspects that the risk of breast cancer is even less for women who are light drinkers of wine, as opposed to other alcoholic beverages. And there may be some protection from breast cancer for light drinkers who take extra folate.

Giovanni de Gaetano, an M.D. and Ph.D. at the Research and Training Center in Biomedical Sciences of Catholic University in Italy, reported on his meta-analysis of the effects of drinking heavily, lightly or not at all on the risk of vascular disease and stroke. Although the studies he reviewed were conducted by different researchers, using different methods and different definitions, almost all of them showed that wine-drinkers had a 34% reduction of vascular risk.

A Glass A Day Keeps the Doctor Away

Who is a "light" drinker as opposed to a "heavy" drinker? Each study has its own operational definition of "light" and "heavy" drinking, which is somewhat arbitrary. (One "drink" is usually defined as five ounces of wine or 12 ounces of beer or one ounce of hard liquor.) Study after study has shown that people who have up to two drinks a day reap the health and longevity benefits of alcohol. They can, in retrospect, be considered "light" drinkers. Those who have more than one or two drinks a day are at risk for higher rates of heart disease and death, and can be considered "heavy" drinkers.

"Alcohol is a double-edged sword," warns Dr. Klatsky. Because of the J-shaped curve, the health benefits of light drinking cannot, in any way, be construed as a license to drink as much as one wants, nor can the dangers of heavy drinking be used to justify complete abstinence. Rather, Klatsky advises everyone to "try to return to an evidence-based approach and keep a balanced view."

That is sometimes easier said than done says R. Curtis Ellison, M.D., of the Boston University School of Medicine. He noted that as late as 1972, the National Institutes of Health refused to publish that part of the Framingham Heart Study that showed positive effects from light drinking.

Confound it!

Earlier epidemiological studies on alcohol, heart disease and mortality did not always control for confounding factors such as smoking. In the past, drinking and smoking inevitably went together like the proverbial horse and carriage, because, as the song goes, you "can't have one without the other." Klatsky pointed out that since smoking itself is associated with an increase in disease and death, studies that did not control for smoking undoubtedly underestimated or missed entirely the health effects of drinking.

Morton Gronbaek, a Danish epidemiologist and physician, further elucidated the problems with epidemiological studies that did not control for other confounding variables such as age, sex, genetic predisposition, degree of exercise, drinking pattern, type of alcohol, diet, risk of heart disease, social class, and accessibility to medical care. Any one of these factors--or some combination of them--could account for whatever protective or pernicious effects are found when correlating the degree of alcohol use with the incidence of heart or other types of disease or mortality.

For example, in the Framingham Heart Study of nurses, those who were over 60 years of age were at higher risk for cardiovascular disease, and were able to lower their risk from moderate drinking. Nurses under 40 were not yet at risk for cardiovascular disease, and so gained no benefit from moderate drinking.

Women reap less benefit from drinking than men, if they drink the same amount. Whereas men who have two drinks a day tend to live longer and have healthier hearts than men who drink less or more, for women the magic number is one drink a day.

About 40% of Caucasians carry a genetic variation, or polymorphism in the gene (ADH3) for the enzyme alcohol dehydrogenase that causes them to oxidize alcohol slowly and thus retain it longer in the body. With light drinking, such lucky slow oxidizers have increased "good cholesterol" or high-density lipids (HDL) and consequently, a lower risk of coronary heart disease. People with fast-oxidizing genotypes benefit much less from alcohol which leaves the body before it has a chance to do much good.

Dr. Ellison says that exercise plus alcohol increases HDLs in both men and women, while leaving "bad cholesterol" or low-density lipids (LDLs) pretty much the same. Maria-Isabel Covas, Ph.D., of the Lipids and Cardiovascular Research Unit of the Municipal Institute for Medical Research in Spain, disagrees, as her research shows that physical activity may counteract the positive effects of moderate alcohol consumption for women.

Drinking patterns, that is, whether a person drinks a lot at once or drinks the same amount spread out over time make a difference. Initial findings indicate that light drinking spread out over time is protective against coronary heart disease, but that drinking the same amount all at once yields no positive effect. The positive effects of alcohol are transient, explains Ellison. One cannot "stock up" on them by drinking a lot in one sitting. To reap a positive effect, one must drink small amounts every day, continually replenishing the supply at a low constant level.

Epidemiological researchers are beginning to study the relationship between different types of alcoholic beverages and health, rather than pouring wine, beer and hard liquor into the same statistical keg. Each differs not only in the degree of alcohol it contains, but also in the remaining non-alcoholic components. When comparisons are made, wine usually comes out looking like a healthier drink than beer or hard liquor. France and Italy--countries in which "drinking" means "wine drinking"--have a lower incidence of mortality from heart disease than the United States and other countries where "drinking" means mostly beer and liquor. However, Ellison reminded everyone that the French may not really be better off, as they do not have an overall lower mortality rate than other countries. The French simply die of causes other than heart disease.

The apparent superior health benefits of wine over beer and liquor are still a topic of debate. Some researchers believe that the alcohol itself is what carries the beneficial effect, whereas others insist that the other components (of wine, in particular) carry at least as much, if not

more, beneficial effect. Dr. Gronbaek says that only when confounding variables--such as socioeconomic status--are not controlled, does wine appear to be healthier than beer or hard liquor. The same J-shaped curve appears for beer or liquor drinking and mortality or other various diseases, though at a slightly lower level than that of wine drinking. But when confounding variables are controlled, the three types of alcohol appear equally healthy. Wine drinkers tend to be of higher socioeconomic status--with all that this implies. (For a detailed discussion, see *Socio-Economic Status and Health in the Industrialized Countries*, Annals of the New York Academy of Sciences, Vol. 896.) They tend to eat healthier diets, containing less meat, butter and other fats. Beer drinkers tend to be of lower socioeconomic status, and to eat less heart-healthy diets. "Is the difference due to the drink or the drinker?" Gronbaek asks.

Stampfer cautions that the benefits of the non-alcoholic components of wine are more speculative than proven. Whatever the "beverage of moderation" happens to be in a particular culture, he says, is the one that is associated with the greatest protection against heart disease. Regardless of the type of alcoholic beverage, most epidemiological studies show that light drinking halves the risk of heart disease, and nearly all studies show a lower incidence of heart attack.

Healthy Hearts Require More Than Drinking

Diet may be the most important confounding factor in epidemiological studies of alcohol and health. Dr. Covas believes that enough high level scientific studies exist to validly conclude that the heart-healthy foods of the Mediterranean diet, in conjunction with daily moderate wine consumption and exercise several times a week, provides protection against heart disease, despite the presence of other risk factors. This, she says, provides the best explanation for a number of paradoxical findings about mortality and heart attacks. In France, Spain and Albania, the incidence of heart attacks is low, despite the presence of risk factors for heart attacks, such as low income, low levels of physical activity, high cholesterol and high levels of smoking.

Covas showed a Mediterranean diet food pyramid, patterned after the familiar food pyramid of the United States Department of Agriculture. Like its American model, the Mediterranean diet food pyramid places cereals, pasta, potatoes and breads at its base. Unlike the six-tiered American pyramid however, the Mediterranean pyramid contains nine tiers. The second tier is composed of fruits and vegetables, followed by olive oil, cheese and yogurt, fish, poultry, eggs, pastries, and at the apex, meat. Off to the side of the pyramid appear a picture of a bottle of wine and a runner.

2. WHAT'S IN THE GLASS? A QUICK COURSE IN WINE CHEMISTRY

The label on a bottle of Cabernet Sauvignon states, "contains 13% alcohol." (Other wines contain similar amounts). So, what's in the other 87%?

Andrew L. Waterhouse, Ph.D. a chemist from the Department of Viticulture and Enology at the University of California at Davis, gave a quick molecular tour of the inside of the flagon. In addition to water and ethanol (alcohol), the main components of wine are organic chemicals of the phenol family. Besides grapes, berries and other vegetables also contain phenols in varying amounts. Phenols give wine its "body" or astringent and bitter taste, as well as its color. Red wine contains more phenols than white wine. As wine ages, the phenols undergo chemical changes, with accompanying changes in color, such as the "browning" of white wine and the deepening color of red wine over time.

Phenols are made of an aromatic ring to which a hydroxyl group (OH) is attached. Phenols in wine are powerful anti-oxidants that destroy free radicals in the body, explained Lester Packer, Ph.D., from the Department of Molecular Pharmacology and Toxicology at the University of Southern California in Los Angeles.

Don't Peel Me A Grape

There are two types of phenols in wine: "flavonoids" and "non-flavonoids." The flavonoids are composed of three aromatic rings, and react readily, binding to other molecules. What these "other molecules" are determines the type of flavonoid--and there are between 6,000 and 8,000 species of flavonoids. A group of flavonoids, called the flavon-3-ols, have been well characterized in wine. Flavon-3-ols are usually concentrated in grape seeds, stems and skin. When these parts of the grape are left in for as long as possible during the wine-making process, more flavon-3-ols end up in the resulting wine than if the seeds, stems and skin are removed earlier.

The non-flavonoids in wine comprise many classes of chemicals including hydroxycinnamates, benzoates, and stilbenes. Much ado has been made in the media about the health benefits of a particular kind of stilbene, called "resveratrol," which is unique to grapes and is not found in other fruits or vegetables. Red wine contains more resveratrol than white wine or grape juice, because the fermentation process removes most of it from fresh grapes, where it is concentrated in the skin. John M. Pezzuto of the College of Pharmacy at the University of Illinois at Chicago, finds that it interferes at several points in a chain of molecular events that lead to cancer.

All Wines Are Not Created Equal

Speaking on the diversity of wine, Fulvio Mattivi, a physician from the Agricultural Institute of San Michele in Italy, says that the relative amounts of the different flavonoids and non-flavonoids vary from one brand and type of wine to another. Even wine made from the same type of grape, raised by the same grower, in the same field, using the same method of processing varies tremendously from one year to the next.

Dr. Waterhouse agrees. "You can't just get a bottle of wine, study it and say, 'This represents all wine,'" he says. For example, expensive wines, made from grapes that received generous amounts of sunlight, may contain four times as many flavonols as cheaper wine. Other phenols in wines can differ from each other by as much as a factor of five, due to differences in soil, growing conditions, type of grape, and processing methods.

Aged Wine Loses Its Vitality

The concentration and molecular structure of the phenols changes as grapes are processed into wine, and as new wine ages into old wine. Oxidation (the addition of an oxygen atom to a molecule) takes place, and the resulting molecules further interact with each other. Resveratrol loses glucose of its molecule. The oak barrel tannins break down and release ellagic acid. After a few months, the hydroxycinnamates begin to break down. The "flavon-3-ols" form bonds with other molecules and change into a form that is not found in the fresh grape.

The good news about all these chemical changes is that as wine ages, the number of anti-oxidizing molecules in it actually increases. Anti-oxidants purge the body of free radicals and are good for us.

The bad news is that, despite the increase in the number of anti-oxidizing molecules over time, their bioavailability decreases. The anti-oxidizing molecules that are formed during aging are

much larger than the original phenols, and thus are not well absorbed in the alimentary canal. After one or two years of aging, the amount of anthocyanin has decreased to about one-sixth of the original level. After five to ten years, wine has lost most of the smaller, and presumably health friendly, phenols. "When we look at very old wine, the only component that stands out is gallic acid," says Waterhouse.

So, ironically, a \$7 bottle of 3-year old wine is a healthier drink than a \$600 bottle of 25-year old wine. (Of course, it may not taste as good!)

What's Not On the Label

Wine makers test all batches of their product for levels of the various phenols. Although a consumer can get that information from a winery's website, the Wine Institute, the trade organization of wine makers, says that it is not on the label because it is "generally considered so esoteric that it's not understood unless by someone in the trade."

Besides, the wine industry is not deliberately trying to produce wines that have high levels of beneficial components. Scientists may conclude that wine has health benefits, but the wine industry is forbidden by law to make any medicinal or therapeutic claims. That [labeling] could be construed as a therapeutic claim.

Nor is the government particularly eager to endorse wine as a healthy beverage, although the Dietary Guidelines, published by the United States Department of Agriculture's Health and Human Services, do include a statement about the health effects of wine. The Bureau of Alcohol, Tobacco and Firearms, which regulates wine labeling, does not allow the USDA statement to appear on wine bottles; it does allow the label to refer consumers to the Dietary Guidelines.

3. HOW PHENOLS AND ALCOHOL WORK

The phenols are among the non-alcoholic components of wine that are thought to carry health benefits. They are powerful anti-oxidants that destroy free radicals in the body. Lester Packer, Ph.D., from the Department of Molecular Pharmacology and Toxicology at the University of Southern California in Los Angeles, explains that a free radical is any molecule that has one unpaired electron in orbit around it. Normally, two electrons circulate on opposite sides of each orbit, balancing each other and rendering the molecule unable to react with other molecules. Ultraviolet radiation and certain chemicals in foods during energy metabolism can knock one of those electrons off, leaving a lone electron behind in orbit. An unpaired electron, Dr. Packer says, is "like a bachelor...it's more reactive." It "seeks" another electron to pair with. If that other electron happens to be part of a protein molecule, such as an enzyme or a hormone, the pairing often destroys or alters the functioning of that protein molecule. When, instead, free radicals acquire an electron from an anti-oxidant molecule, such as a phenol, then no essential protein molecules are disturbed.

Of course, once the anti-oxidant molecule loses an electron, it, in effect, becomes a free radical itself! Not a problem, assures Packer. When the newly formed free radical is a phenol, the unpaired electron must circle the ring of atoms, rather than remain in one place, as electrons do in original free radicals. These second-generation former-anti-oxidants-now-free-radicals are like old bachelors: They may still be single, but they are not that bent on seeking a mate. These molecules are less reactive and less available to bind with other molecules or steal their electrons.

Wine and a Meal

Fulvio Ursini, a physician from the Department of Biochemistry at the University of Padova in Italy, explains why the Mediterranean diet is so healthy: It contains fewer oxidizable foods and less iron than other diets. (Iron promotes oxidation.) At the same time, it has more anti-oxidants and more polyphenols, especially when accompanied by a glass of red wine, as is the custom in the countries that follow this diet.

It is not enough simply to have one or two drinks a day, says Dr. Ursini. In order to reap the heart-protective benefit of light drinking, one must have those drinks during the meal. "Wine taken with food prevents post-prandial increases of LDL susceptibility to copper-induced peroxidation," he says.

Put simply, without wine, the level of LDL increases dramatically immediately after eating, due to the sudden influx of fats or lipids that become oxidized. With wine, oxidation is dramatically decreased, because the anti-oxidant polyphenols of the wine are present to act upon the lipids from the meal before the pernicious chain reaction starts. Wine ingested apart from a meal has no food to act upon, and so, provides little or no protection against oxidation.

Hydroperoxides must be present for this chain reaction to start, but Dr. Ursini is still uncertain as to where they originate--perhaps from the food itself. Once lipids are oxidized--even a little bit--hydroperoxides are produced as byproducts. These hydroperoxides, in turn, promote further oxidation, and the process escalates.

Dr. Ursini is experimenting with in vitro models of atherosclerosis and has observed that oxidized lipids of LDL damage the fibers of the arteries, which could account for the development of atherosclerosis. "Remarkably, wine prevents this damage, Ursini says. He has determined that after a meal, the level of a kind of "super LDL" increases. This molecule has a different structure in space from regular LDL: It includes oxidized lipids and cholesterol, and a tryptophan segment "sinking in the middle of the molecule." Ursini calls it "LDL-minus" because its somewhat different conformation gives it more negative surface charge. This, he says, is the key factor in oxidation and the genesis of atherosclerosis. LDL-minus damages the structure of lipoproteins. Wine, taken with a meal, prevents regular LDL from morphing into LDL-minus.

"Thinning the Blood"

Besides curtailing oxidation, red wine appears to decrease the adhesion of blood platelets to the walls of the arteries and veins and to collagen. De Gaetano described his clinical and in vitro animal studies of the effect of wine's polyphenols on atherosclerosis and on thrombosis, or blood clots. De Gaetano fed rats a high fat and high cholesterol diet, resulting in high triglycerides, high cholesterol, and high "Factor VII", a key element in blood coagulation and a biochemical marker for thrombotic tendency. When Factor VII activates, it "starts an enzymatic cascade which ends up in the formation of a clot," explains de Gaetano. After five months on this diet, thrombosis was artificially induced in the rats. To test the effect of wine's polyphenols, apart from the alcohol content, de Gaetano then gave the rats alcohol-free red wine. Thrombosis decreased, although the levels of triglycerides and cholesterol remained the same. De Gaetano believes that the nitric oxide (NO) in wine protected the rats against thrombosis. When NO was inhibited (by the administration of an ester called, "L-NAME"), the protective effect of wine disappeared.

Don't Spit Out the Seeds

Why is it that the best part of a fruit or vegetable is so often the part that we throw away? At

least two researchers who study grape seed extract (GSE) have observed it to have powerful positive effects whether in vitro, in rats, or in humans.

Harry G. Preuss, M.D., of the Department of Physiology at Georgetown University, found that administering GSE reduced blood pressure in normal rats beyond the reduction already achieved by administering chromium. Both GSE and chromium increased insulin sensitivity and lowered T-bar formation, that is, a measure of the damage that free radicals wreak on cell membranes. GSE reduced blood pressure in hypertensive rats even more so, though for these rats, there appeared to be no change in insulin level.

The rats were later divided into an experimental group that received GSE, and a control group that did not. They were monitored for a year, which is equivalent to about 26 years in humans. These young adult experimental rats never developed high blood pressure, despite their advancing age. The control rats did. There was no evidence of toxicity.

In humans, high blood pressure, along with Type II diabetes, hyperlipidemia and obesity occur together so frequently with age that they have been dubbed, "Syndrome X." (See "The Metabolic Syndrome X," *Annals of the New York Academy of Sciences*, Vol. 892.) Besides being harmful conditions per se, they are also risk factors for atherosclerosis and coronary vascular disease. To see if GSE or chromium had the same beneficial effects on humans as it did on rats, Dr. Preuss conducted a double blind, placebo control study of 40 subjects. For two months, some received GSE alone, some received chromium alone, and some received a combination of both. For those on the combination dose, LDL showed a decrease over time, while HDL remained the same, and triglycerides decreased slightly, though not enough to achieve statistical significance. A checklist of physical symptoms revealed no adverse effects.

A novel form of grape seed extract, fortified with Vitamins C and E, has been tested in vitro, in animals and in humans by Debasis Bagchi, Ph.D., of Creighton University School of Pharmacy and Allied Health Professions in Nebraska. After pretreating mouth cells with Vitamins C and E, and then deliberately damaging them with tobacco, Dr. Bagchi found that 42% of them were protected against tobacco-induced apoptosis, or programmed self-destruction. With cells that were pretreated with grape seed proanthocyanidin extract, or GSPE, the protective effect rose to 82%. Unlike most molecules aimed at treating cancer, GSPE was toxic only to the cancerous cells, while it fostered growth and viability in the normal cells.

Alcohol in Wine

So much attention has been paid to the health benefits of the non-alcoholic components of wine that it is easy to overlook the cardio-protection provided by alcohol or "ethanol" itself. James M. Downey, Ph.D., a physiologist from the University of Southern Alabama, has found that acute exposure to alcohol reduces "osmotic fragility," an index of cell injury. The more heart cells that are protected from injury during a heart attack, the better the condition of the heart afterwards.

Downey has observed that when an excised animal heart experiences five minutes of "ischemia" or restricted blood flow, it immediately launches into an adaptive mode of functioning, such that it is better able to resist another, later episode of ischemia. In effect, the first episode of ischemia "inoculates" the heart against the second episode. During this adaptive period, "signal transduction" within the heart cells is being triggered by receptors on the cell surfaces, though Downey has not fully deciphered the significance of this. This protective phase lasts for about an hour, before the heart reverts to its previous, normal state. Twelve hours after the inoculating ischemia, certain genes begin to produce proteins that provide a second, lower level of protection that lasts for about four days.

Downey regards the first inoculating episode of ischemia as a kind of "preconditioning." It is activated by adenosine and has been observed to occur in humans: Patients who have a heart attack after an episode of angina or transient ischemia are more likely to survive than patients who experienced no such previous episodes.

For unknown reasons, alcohol has a similar preconditioning effect on the heart. If an excised animal heart is exposed to five minutes of alcohol before ischemia is administered, and then the alcohol is washed out of the cells, more of the heart's cells are able to survive the ischemia. The same procedure conducted on live, intact animals also protects their hearts from subsequent ischemia. The trick though, is to rid the animal's blood of alcohol before administering the ischemia. Alcohol that remains in the blood during the ischemia actually works against its own protection as well as other preconditioners.

Theoretically, this means that if a human drank alcohol prior to a heart attack, more of the heart cells would survive. However, the timing and amount of alcohol would have to be very carefully regulated so that the alcohol would be out of the blood by the time of the actual heart attack. It takes about 50 minutes from the time of imbibing for blood alcohol levels to fall enough for this to work. If any alcohol remained during the heart attack, it would not only not help cells to survive, but would interfere with the body's own natural preconditioners. Since one cannot know if or exactly when a heart attack is going to occur, it would be rather difficult-perhaps impossible-to know when to drink the alcohol in order to gain protection.

It is possible though that daily light drinking provides the body with just enough alcohol to constantly maintain that second, lower level of protection against ischemic cell damage that Downey observed in the four-day period following the initial administration of alcohol. The only time light drinking would inhibit the body's natural protection would be for about one hour after drinking. Perhaps this is one explanation of the finding of lower rates of heart disease and death from heart attacks found among light drinkers.

4. SHOULD I DRINK, DOCTOR?

Assuming that the evidence about the beneficial effects of light drinking is valid, the question remains: What should be done with this evidence? Should an extra tier for wine be drawn into the original food pyramid? Should non-drinkers be encouraged to start drinking? If so, should they be advised to drink alcoholic beverages that are associated with light drinking (such as wine) rather than those that are associated with heavy drinking (such as hard liquor or beer)? Should women who are at risk for breast cancer be included with those who are advised to drink in moderation? Should public health organizations recommend light drinking? Should physicians tell patients, "Have a glass of wine and call me in the morning?"

Stampfer emphasized that the answers to these questions are not simple yes's or no's, but rather depend on who is asking the questions.

Stampfer stresses that certain people should never be advised to drink, regardless of the health benefits. These include children, teenagers, and anyone with a past alcohol or other substance abuse problem or a family history of alcoholism. They should be advised to abstain entirely. Similarly, patients who suffer from certain medical conditions should be informed about the hazards that drinking might present to them, despite what they might have heard about the benefits drinking holds for other people. Patients who must take certain medications should be warned about dangerous interactions between alcohol and their medications. People whose

religion or personal sense of morality forbids drinking should not be argued or pressured into drinking.

That still leaves the vast majority of non-teetotaling adults who are neither ill nor at risk for alcoholism. They, Stampfer says, should be told to consult their doctor. But what should their doctor tell them? Should physicians advise them all to drink in moderation? Klatsky and his colleague, Roger R. Ecker, also a physician from Kaiser Permanente Medical Center, have put together a "decision tree" for health professionals who are asked, "Doctor, should I have a drink?" By choosing a category at each branch, a physician can trace a customized path down the decision tree for a particular patient, and thus be able to give that patient tailor-made advice about whether or not to drink lightly.

Ellison says that there is no actual data on the risk of a non-drinker developing a drinking problem as a result of being advised to have a glass of wine at dinner. Since light drinking would benefit primarily older people (who are at risk for cardiovascular and other diseases) rather than younger people (most of whom are not at risk), Klatsky has done some hypothetical, cost-benefit, number-crunching on the data of people over 65 years of age. Even if 5% of them did become alcohol abusers as a result of medical advice to have a glass of wine at dinner, the mortality rate in this age group on the whole would be lower than if they had not been advised to engage in daily light drinking.

The Bottom Line

The effect of alcohol and wine in health and disease is complex and fraught with caveats, exceptions and uncertainties. Light consumption of alcohol, particularly red wine, (though that is not definite), can protect some people (but not others) against some diseases (but not others), provided it is consumed on a daily basis during a meal, especially a Mediterranean diet meal.